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Biomimetic surface modification on polyacrylonitrile-based asymmetric membranes via direct formation of phospholipid moieties

Xiao-Jun Huang [a,b], Zhi-Kang Xu [a,b,*], Xiao-Dan Huang [c], Zhen-Gang Wang [a,b], Ke Yao [c]

[a] *Institute of Polymer Science, Zhejiang University, Yu Gu Road 38#, Hangzhou 310027, People's Republic of China*

[b] *Key Laboratory of Macromolecule Synthesis and Functionalization, Zhejiang University, Ministry of Education, Hangzhou 310027, People's Republic of China*

[c] *Medical College, Zhejiang University, Hangzhou 310027, China*

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Abstract

To improve the antifouling property and biocompatibility for polyacrylonitrile-based asymmetric membranes, phospholipid moieties were directly anchored on the poly(acrylonitrile-*co*-2-hydroxyethyl methacrylate) (PANCHEMA) membrane surface through the reaction of hydroxyl groups and 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) followed by the ring-opening of COP with trimethylamine. Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, scanning electron microscopy and water contact angle measurement were employed to confirm the conducted surface modification. Water and protein solution filtration tests plus cell adhesion measurement were used to evaluate the antifouling property and the biocompatibility of the membranes. It was found that the content of the phospholipid moieties on the membrane surface, which can be mainly modulated by the content of reactive hydroxyl groups in PANCHEMA, has a great influence on the performances of the studied membranes. With the increase in the phospholipid moieties content at the modified membrane surface, the hydrophilicity and biocompatibility on the basis of water contact angle and macrophage adhesion can be improved significantly. Furthermore, the modified membranes show higher water and protein solution fluxes, and better flux recovery after cleaning than those of the original PANCHEMA membranes. All these results reveal that the antifouling property and biocompatibility of PANCHEMA membrane could be enhanced obviously by the introduction of phospholipid moieties on the membrane surface.
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Keywords: Asymmetric membrane; Surface modification; Phospholipid moieties

1. Introduction

Membrane filtration is increasingly used for the separation and purification of protein-containing solutions. But fouling is one of the critical factors determining the effectiveness of the membrane process. This fouling is mainly attributed to the concentration polarization and protein deposition on the membrane surface. Concentration polarization, resulting from concentration gradient due to solute accumulation near the membrane surface, is reversible in nature and independent of the properties of the membrane. While the protein adsorption or deposition, which will lead to significant loss of performance (selectivity and permeation flux) and can have a serious impact on the efficiency and economics of the protein recovery process, is irreversible in nature [1]. In order to reduce the irreversible protein fouling in the filtration process, polymeric membranes should possess specific functional properties such as hydrophilicity and low interactions with proteins and cells [1–3].

Polyacrylonitrile (PAN) and acrylonitrile-based copolymers, which possess excellent membrane forming property and good thermal and mechanical stability, have been successfully applied as membrane materials in the fields of water treatment, pervaporation, gas separation, biochemical product purification, and biomedical applications [4–8]. In particular, PAN hollow fiber membranes, such as AN69 (produced by HOSPAL, fabricated from an acrylonitrile/methallyl sulfonate copolymer), have already been used as dialyzers that enable proteins with relative low molecular weight removals and high-flux dialysis therapy [9]. However, the moderate hydrophilicity and relatively poor biocompatibility for these membranes limit their further applications in biomedicine and bioengineering. It has been well known that increasing the hydrophilicity of the membrane surface can reduce protein fouling and improve biocompatibility for common membranes [8,10–13].

* Corresponding author. Address: Tel.: +86 571 8795 2605; fax: +86 571 8795 1773.

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Therefore, many methods have been reported to develop PAN-based membranes with improved biocompatibility and antifouling properties or both [11–14]. For example, copolymerizing acrylonitrile with hydrophilic monomers and grafting hydrophilic monomers on the membrane surface have been described to improve the hydrophilicity and biocompatibility of PAN membrane [15–18]. However, even the material surface is hydrophilic, the interaction of protein with the material surface is entropically driven and the adsorption may also be irreversible because the accumulated number of direct contacts between protein fragments and the surface may be too large to allow desorption [19,20].

Objective for our study is to entrust a novel biomimetic surface to the PAN-based asymmetric membranes by introducing phospholipid moieties onto the PANCHEMA membrane surface. The fundamental concept is inspired by the mimicry of a biomembrane, which is mainly constructed of phospholipid and phosphorycholines. Polymers derived from phospholipid analogues have been shown to reduce protein adsorption significantly as their hydrated surfaces are able to interact with proteins without inducing conformational changes in their three-dimensional structures, unlike many other polymers [21]. To endow synthetic polymers with biomimetic properties, various vinyl-containing phospholipids and their polymeric analogues were synthesized [22]. Potential applications of these phospholipid-containing polymers to modify the surface of separation membranes (such as cellulose acetate, poly(vinylidene dichloride), polysulfone, polyurethane, polyethylene, and poly(vinyl chloride)) by blending or coating were also explored [23–26]. In this work, to improve the antifouling property and biocompatibility for polyacrylonitrile-based membrane, PANCHEMAs with different content of 2-hydroxyethyl methacrylate (HEMA) were fabricated into asymmetric membrane by the immerse precipitation phase inversion method. As schematically described in Fig. 1, phospholipid moieties were directly anchored onto the PANCHEMA asymmetric membrane surface via a reaction of hydroxyl groups on the membrane surface with 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) followed by a ring-opening reaction of COP with trimethylamine. After the generation of phospholipid moieties on the membranes surface, the nascent and modified membranes were compared with respect to their hydrophilicity, cell attachment, water and protein solution permeation as well as flux recovery after protein solution filtration by chemical cleaning.

2. Experimental

2.1. Materials

Poly(acrylonitrile-*co*-2-hydroxyethyl methacrylate) (PANCHEMA) with different HEMA contents, designated as PANCHEMA06, PANCHEMA09 and PANCHEMA18 in the following text, were synthesized by water phase precipitation copolymerization in our laboratory. Details for the characterization of the copolymers were described in our previous work [27]. 06, 09 and 18 in the designation indicate that the content of HEMA in the copolymer are 6.4, 9.3, and 17.8 mol%, respectively. Trimethylamine (TMA, Aldrich, USA) and bovine serum albumin (BSA, pI=4.8, M_w=66 kDa) were commercial products and used as received. Acetonitrile, tetrahydrofuran (THF), triethylamine (TEA), phosphorus trichloride and ethylene glycol were purchased from Shanghai Chemical Co. of China and distilled before use. Dichloromethane and benzene were dried by distillation from metal natrium. One gram per litre and 500 ppm BSA solutions were prepared in a phosphate buffered saline (PBS) solution at pH 7.4. Ultrafiltrated water was used as the nonsolvent (coagulant). Other reagents were analytical grade and were used without further purification. 2-Chloro-2-oxo-1,3,2-dioxa-phospholane, bp 99–101 °C/1 mm Hg (lit.: bp 79 °C/0.4 mm Hg), was synthesized according to the method of Lucas et al. [28] and Edmunson [29].

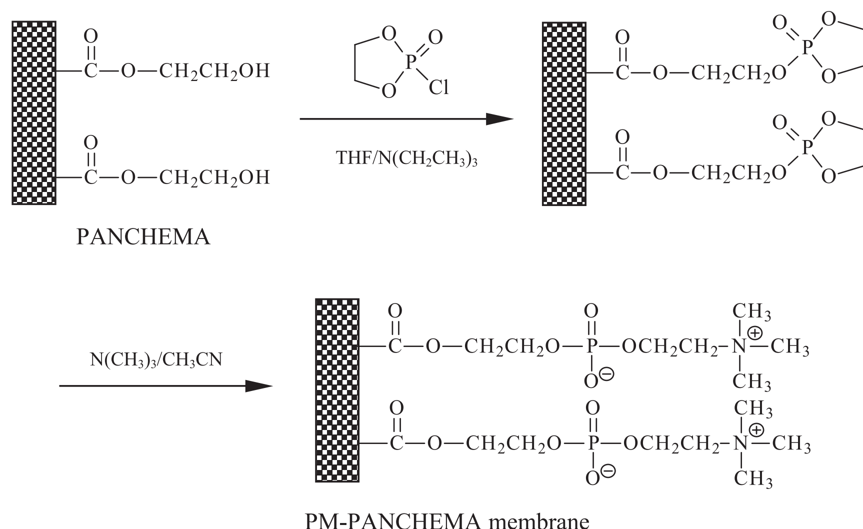

Fig. 1. Schematic representation for the direct introduction of phospholipid moieties on the PANCHEMA membrane surface.

2.2. Fabrication of PANCHEMA membranes

The PANCHEMAs were used as membrane materials. DMSO and deionized water were used as solvent and nonsolvent additive, respectively. These copolymers were dried for at least 3 h at 60 °C in a vacuum oven and then dissolved in DMSO at about 80 °C for 24 h followed by the addition of 10 wt% deionized water with vigorous stirring to form 10 wt% homogeneous solutions. After air bubbles were removed completely, the solutions were cast onto clean glass plates using a casting knife with a 150 μm gate opening. The nascent membrane was placed in atmosphere (25 ± 1 °C, 45–50% relative humidity) for 10 min and then immersed in 30 ± 1 °C ultrafiltrated water for 24 h. After precipitation, the membranes were peeled off and preserved in a 5 vol% glycerin aqueous solution for further use.

2.3. Introducing phospholipid moieties onto the PANCHEMA membranes

The process was the same one as described in our previous work [30]. PANCHEMA membranes were first washed with a water–ethanol–hexane sequence, and then dried for 24 h at 40 °C under vacuum. To anchor phospholipid moieties onto the membranes surface, the dry PANCHEMA membrane (3.5×3.5 cm^2), 50 mL THF, and a designated amount of triethylamine (TEA) were placed into a thoroughly dried 200 mL single necked pressure-resistant flask. After the solution was cooled to a range of −5 to 0 °C, calculated amount of COP dissolved in 50 mL of dry THF were rapidly injected into the flask. Then, the flask was sealed to keep water out. Subsequently, the mixture was shaken gently for 2 h in the temperature range of −5 to 0 °C. After the reaction was completed, the solution in the mixture was rapidly poured out of the flask under dry argon atmosphere, and then 5 mL of anhydrous TMA dissolved in 100 mL cooled and dry acetonitrile was rapidly injected into the flask. The pressure-resistant flask was sealed and shaken gently for 24 h at a temperature of 60 °C. Then, the resultant membrane was taken out and washed with deionized water to remove the absorbed chemical residues on the membrane surface. Finally, the membrane was washed with a water–ethanol–hexane sequence and dried at 40 °C in a vacuum oven.

2.4. Membrane characterization

To analyze the chemical changes between the original and the phospholipid-modified PANCHEMA (PM-PANCHEMA) membranes and confirm the introduction of phospholipid moieties on the membrane surface, attenuated total reflectance Fourier transform infrared (FT-IR/ATR) spectra were measured on a Vector 22 spectroscope (Brucker, Switzerland).

X-ray photoelectron spectroscopy (XPS) was conducted on a PHI 5000C ESCA System (PHI Co., USA) employing Al Kα excitation radiation (1486.6 eV) with an electron take off angle of 45° relative to the sample plane, to confirm the chemical structure of the PM-PANCHEMA and assess the near-surface composition of the membranes. Typical characteristics of the PM-PANCHEMA membranes are shown in Table 1.

The morphologies of the studied membranes were inspected by scanning electron microscopy (SEM) using a Sirion field emission SEM (FEI, USA). For this purpose, membrane samples were washed with a water–ethanol–hexane sequence, dried at room temperature, frozen in liquid nitrogen, and fractured to obtain tidy cross-section. After the samples were sputtered with gold, the surface and cross-section morphologies of the membranes were observed on the scanning electron microscope.

2.5. Hydrophilicity measurement

The hydrophilicity of the membrane surface was characterized on the basis of water contact angle measurement. Using a sessile drop method, water contact angle was measured at room temperature by a contact angle goniometer (OCA20, Dataphysics, Germany) equipped with video capture. A total of 5 μL of deionized water was dropped on a dry membrane with a micro syringe in atmosphere. At least 10 contact angles were averaged to obtain a reliable value.

2.6. Macrophage adhesion

Murine macrophage suspension was prepared according to the following process. The suspension was isolated from freshly killed mice using chloroform. The skin was sprayed with alcohol and the abdomen was opened. Ten millilitre sample of Roswell Park Memorial Institute (RPMI) 1640 containing 10% foetal bovine serum (FBS), 100 g/mL penicillin, and 100 μm/mL streptomycin, was injected into the peritoneal cavity, and then the abdomen was gently massaged by fingers for 5 min. The peritoneum was carefully punctured, and then the washings were removed by a sterile pipet and placed in a sterile container to be centrifuged at 1000 rpm for 10 min to collect the macrophages. The macrophages obtained were grown in RPMI 1640 to obtain the macrophage suspension in which the cell concentration was 1×10^6 cells/mL. The membrane (10×10 mm^2) was cleaned sequentially in an ultrasonic bath of ethanol solution for 10 min and then rinsed in phosphate buffer saline (PBS). Then, the samples were immersed in physiological saline (pH 7.4) to recondition for several hours. The cell suspension was inoculated on the membrane surface to assess the cell attachment. The incubation period was 48 h for the cell attachment test in a humidified atmosphere of 5% CO_2 in air at 37 °C. After that, the supernatant was removed, and the membranes were washed cautiously five times using PBS (pH 7.2) prior to fixation. The adherent cell density on the membrane surface was quantified on the basis of measurements obtained visually from at least five randomly selected fields using an Olympus TE300 phase contrast optical microscope.

2.7. Permeation flux measurement

The solution reservoir was initially filled with ultrafiltrated water, and the membrane about 9.10 cm^2 was installed into the

Table 1
Typical characteristics of the PANCHEMA and the PM-PANCHEMA membranes

Membranes	[η] (dL/g)	HEMA content in PANCHEMA[a] (mol%)	Phospholipid moieties on membrane surface[b] (mol%)	Contact angle[c] (°)
PANCHEMA06	3.22	6.4	–	57.4 ± 0.7
PANCHEMA09	3.19	9.3	–	55.9 ± 0.8
PANCHEMA18	3.04	17.8	–	53.8 ± 0.6
PM-PANCHEMA06	–	–	6.09	42.3 ± 0.5
PM-PANCHEMA09	–	–	9.19	40.1 ± 0.6
PM-PANCHEMA18	–	–	17.1	33.2 ± 0.5

[a] The content of HEMA in PANCHEMA was calculated from ^{1}H NMR.
[b] The content of phospholipid moieties on the membrane surface was calculated from XPS.
[c] Measured by sessile drop method.

permeation cell. Each membrane was precompacted for 30 min at 0.15 MPa. Then, the pressure was lowered to 0.08, 0.10 and 0.12 MPa, respectively, and the flux of ultrafiltrated water (J_w) was measured till consecutive recorded values differed by less than 2%. Next, a 1.0 g/L BSA aqueous solution was added to the reservoir and the filtration experiment was performed at the corresponding pressure, the permeation flux at the end of BSA solution filtration was denoted as J_p. To confirm the water flux recovery property of these BSA permeated membranes, the membranes were cleaned by vibrating in a 0.1 M NaOH solution for 2 h and washing with ultrafiltrated water for three times after BSA solution filtration, and then the water flux (J_R) was measured at the same pressure. The reported data was the mean value of triplicate samples for each membrane. The relative flux reduction (RFR) and the flux recovery ratio (FRR) were calculated as follow:

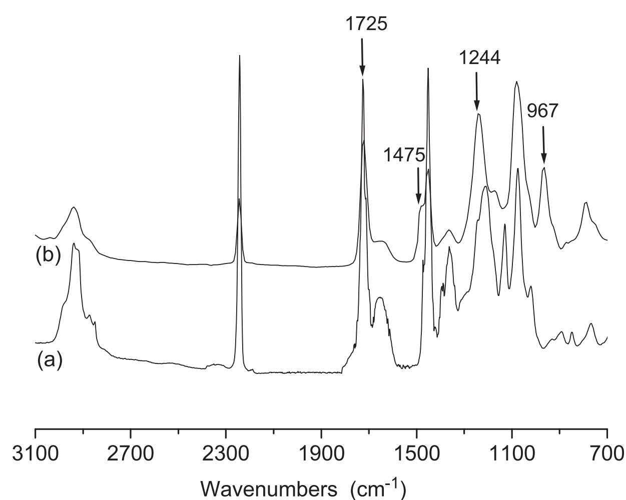

Fig. 2. FT-IR/ATR spectra of PANCHEMA (a) and PM-PANCHEMA (b) membranes.

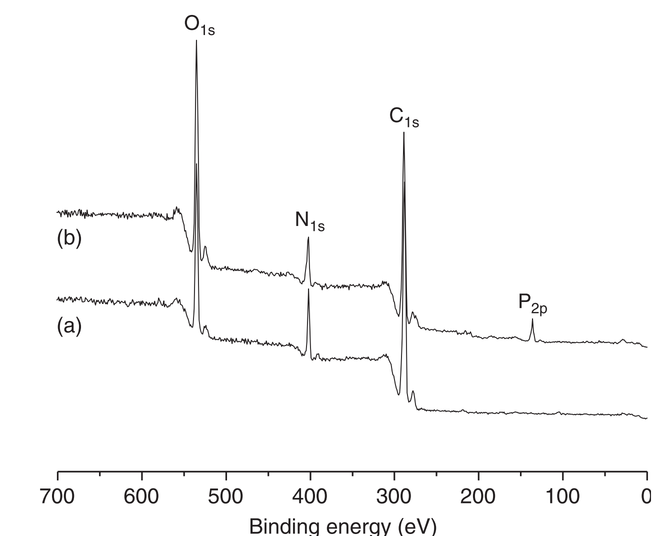

Fig. 3. Survey XPS spectra of PANCHEMA (a) and PM-PANCHEMA (b) membrane surface.

$$\mathrm{RFR}(\%) = (1 - J_p/J_w) \times 100$$

$$\mathrm{FRR}(\%) = (J_R/J_w) \times 100$$

A 500 ppm BSA solution was used for the solution rejection (R) study. The BSA concentration in the feed and filtrate were analyzed using a spectrophotometer (Shimadzu, UV-1601) at 280 nm. The solute rejection was calculated by

$$R(\%) = (1 - C_p/C_f) \times 100$$

where C_p and C_f are the BSA concentration in permeate and feed, respectively. The solution rejection was tested at the transmembrane pressure of 0.8, 0.1 and 0.12 MPa, respectively. All results were the average of two parallel modules.

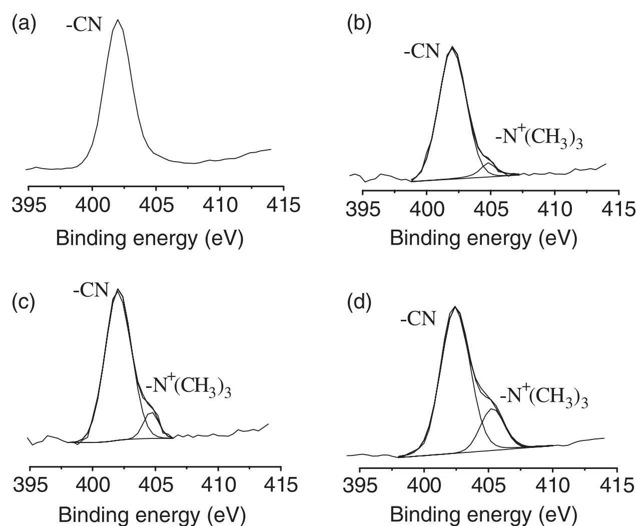

Fig. 4. Core-lever XPS spectra of N_{1s} for PANCHEMA (a); PM-PANCHEMA06 (b); PM-PANCHEMA09 (c) and PM-PANCHEMA18 (d) membrane surface.

3. Results and discussion

3.1. Chemical and morphological changes of the membranes

Surface modification of common polymer membranes is an attractive approach to improve the surface properties in a defined selective way without affecting any bulk properties [31–33]. In our work, as schematically described in Fig. 1, phospholipid moieties were directly anchored onto the asymmetric membrane surface by chemically reactions. Fig. 2 shows the FT-IR/ATR spectra of the studied membranes. It can be seen that, compared with the spectrum of PANCHEMA membrane, there is a series of new adsorption peaks at 1475, 1244, and 967 cm^{-1} in the spectrum of the PM-PANCHEMA membranes, which ascribe to the stretching vibrations of $–CH_3$, –O–P–O–, and $–N^+(CH_3)_3$ groups in the phospholipid moieties, respectively. To further verify the chemical structure of PANCHEMA and PM-PANCHEMA, XPS spectra were measured from the membrane surface. In the case of the PANCHEMA membrane (Fig. 3), two strong peaks at 285 and 525 eV can be observed, which are attributed to C_{1s} and O_{1s}, respectively. Another peak at 401 eV ascribable to N_{1s} in the nitrile group is also obvious. For the PM-PANCHEMA membrane, on the other hand, a new peak appears at 137 eV, which is due to P_{2p} in the phospholipid moiety. Furthermore, to calculate the content of phospholipid moiety on the membrane surface, high resolution spectra for the PANCHEMA and PM-PANCHEMA membranes corresponding to N_{1s} are shown in Fig. 4. There are two components in the N_{1s} core level spectrum of the phospholipid modified membranes. The first one at 402 eV is attributed to N_{1s} in nitrile group. The second one (405 eV) is due to N_{1s} in $–N^+–(CH_3)_3$ of phospholipid moiety. The content of phospholipid moiety on the membrane surface is summarized in Table 1. It was found that the phospholipid moiety has an obvious increase with the increase of HEMA content in the copolymer membrane. When the

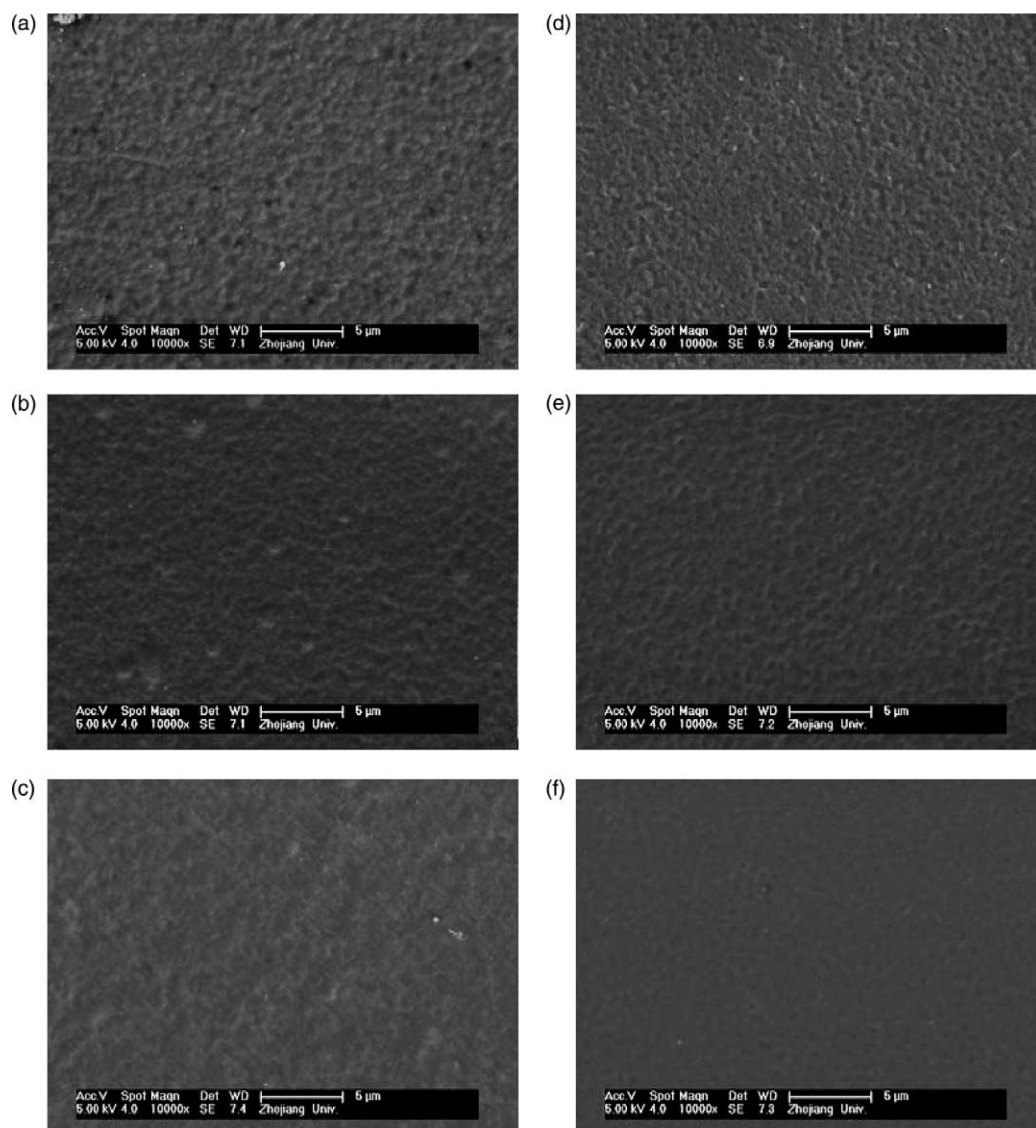

Fig. 5. SEM photographs of PANCHEMA and PM-PANCHEMA membrane surface: (a) PANCHEMA06; (b) PANCHEMA09; (c) PANCHEMA18; (d) PM-PANCHEMA06; (e) PM-PANCHEMA09; (f) PM-PANCHEMA18.

HEMA content in PANCHEMA increases from 6.4 to 17.8 mol%, phospholipid moiety on the membrane surface shows an increase from 6.09 to 17.1 mol%. All these results confirm that the process described in Fig. 1 could be used to generate phospholipid moieties on the PANCHEMA membrane surface.

The morphologies of the external surface and the cross-section for the resultant membranes were observed by SEM at a 10,000× magnification. As can be seen from Figs. 5 and 6, the membranes possess typical asymmetric structure consisting of a dense skin surface and a finely porous (sponge-like) sub-layer. When PANCHEMAs concentration is 10 wt%, addition of 10 wt% water can completely suppress the formation of macrovoids. On the other hand, both PANCHEMA and PM-PANCHEMA membranes have similar surface and cross-section morphologies. As for the modification reaction temperature is far lower than the T_g of PAN (105–115 °C) and phospholipid moieties are chemically anchored on the membrane surface through covalent bonding, it seems that no obvious morphological change could be observed on the membrane surface and in the bulk.

3.2. Surface properties of the membranes

Water contact angle (WCA) has been commonly used to characterize the relative hydrophilicity or hydrophobicity of the membrane surface. For membranes with comparable structures, relatively low WCA value normally means high hydrophilicity. Static WCAs for the studied PANCHEMA and PM-PANCHEMA membranes are listed in Table 1. It can be seen that the WCA decreases gradually from 57.4±0.7 to 33.2±0.5 with increasing phoshpolipid moieties on the PM-PANCHEMA membrane surface from 0 to 17.1 mol%. This is due to the contribution of the zwitterions in phospholipid moieties on the membrane surface.

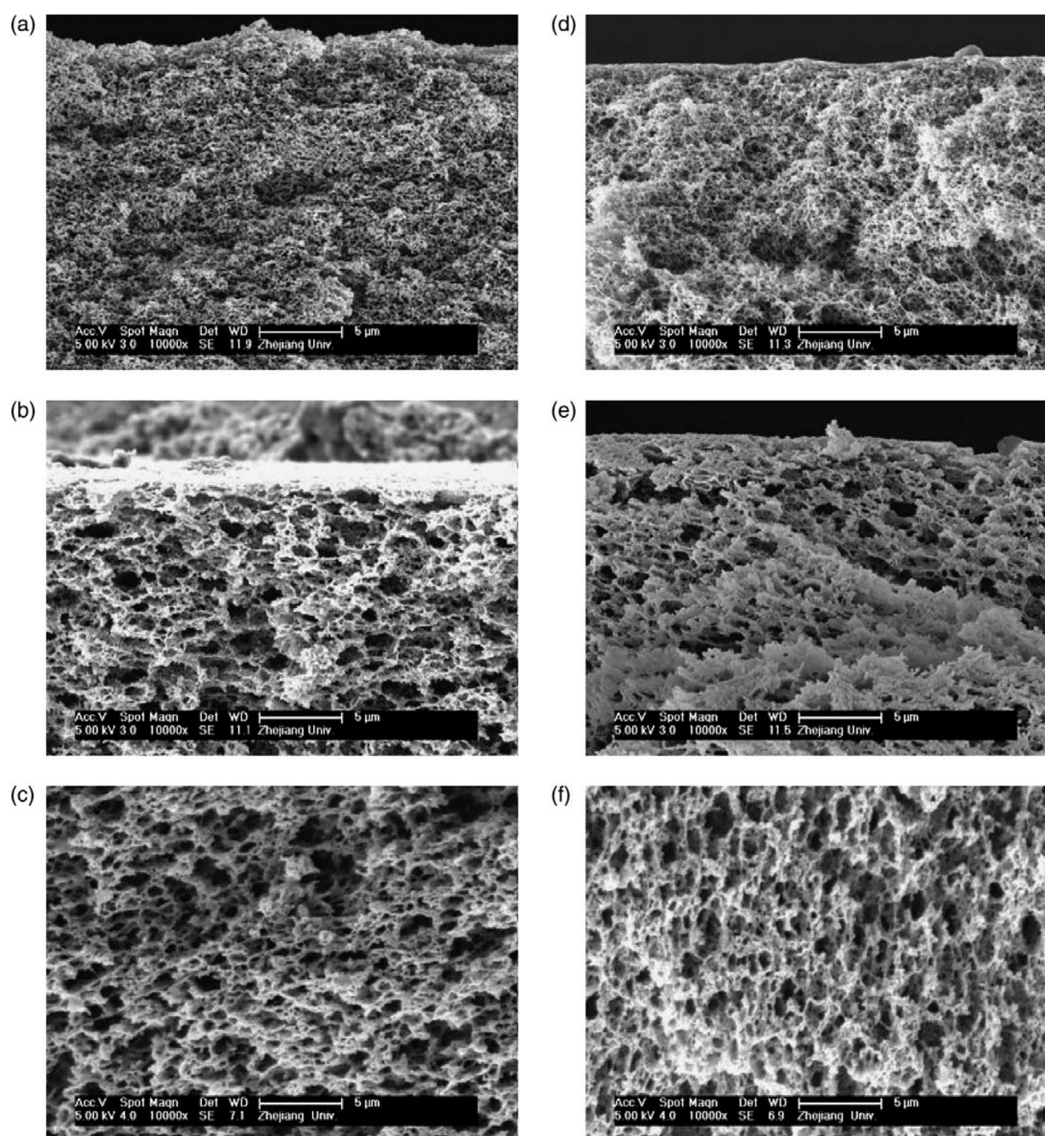

Fig. 6. SEM photographs of PANCHEMA and PM-PANCHEMA membrane cross-section: (a) PANCHEMA06; (b) PANCHEMA09; (c) PANCHEMA18; (d) PM-PANCHEMA06; (e) PM-PANCHEMA09; (f) PM-PANCHEMA18.

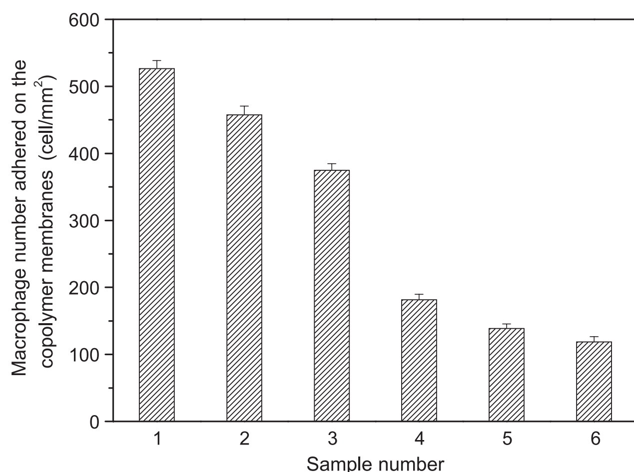

Fig. 7. Adhesion of macrophage on the PANCHEMA and PM-PANCHEMA membrane surface: (1) PANCHEMA06; (2) PANCHEMA09; (3) PANCHEMA18; (4) PM-PANCHEMA06; (5) PM-PANCHEMA09; (6) PM-PANCHEMA18.

The host-foreign-body response is a well-known interfacial phenomenon when polymeric materials come into contact with living organisms. A common component of this response is the presence of adherent macrophages, which fuse to form foreign-body giant cells (FBGCs) on the surface of polymeric material. It has been shown that these adherent macrophages can cause biodegradation in the form of cracking and pitting through the release of bioactive agents [34]. Based on this concept, an ideal biomaterial that is designed for blood-contacting applications should inhibit the adhesion, activation, and subsequent fusion of macrophages into FBGCs, thereby preventing the structural, mechanical, or functional failure of the biomaterial. Herein, macrophage adhesion was measured to characterize the biocompatibility for the modified membranes and typical results are shown in Fig. 7. It demonstrates clearly that the number of macrophage adhered on all the PM-PANCHEMA membranes is significantly decreased as compared with that on the PANCHEMA membranes, which indicates that the phospholipid moieties on the membrane surface could induce the reduction of macrophage adhesion. This phenomenon is due to the phosphorylcholine group, a typical phospholipid polar group located at the outer cell membrane and can provide hydrated surface for the polymeric membrane in an aqueous medium [22,23,35]. Thus, cell adsorption can be effectively inhibited and the conformation of cell does not change even

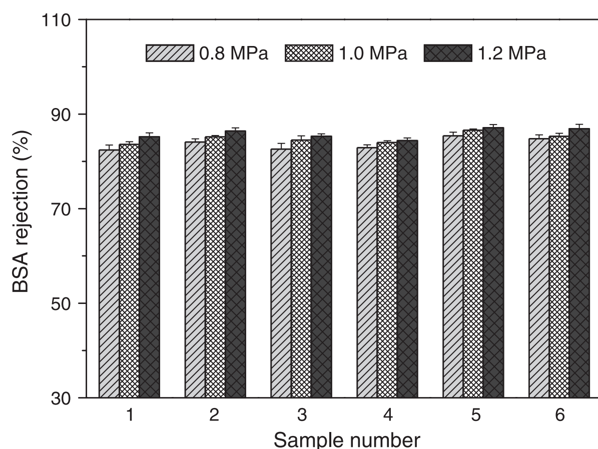

Fig. 8. Comparison of BSA rejection for PANCHEMA and PM-PANCHEMA membranes: (1) PANCHEMA06; (2) PANCHEMA09; (3) PANCHEMA18; (4) PM-PANCHEMA06; (5) PM-PANCHEMA09; (6) PM-PANCHEMA18.

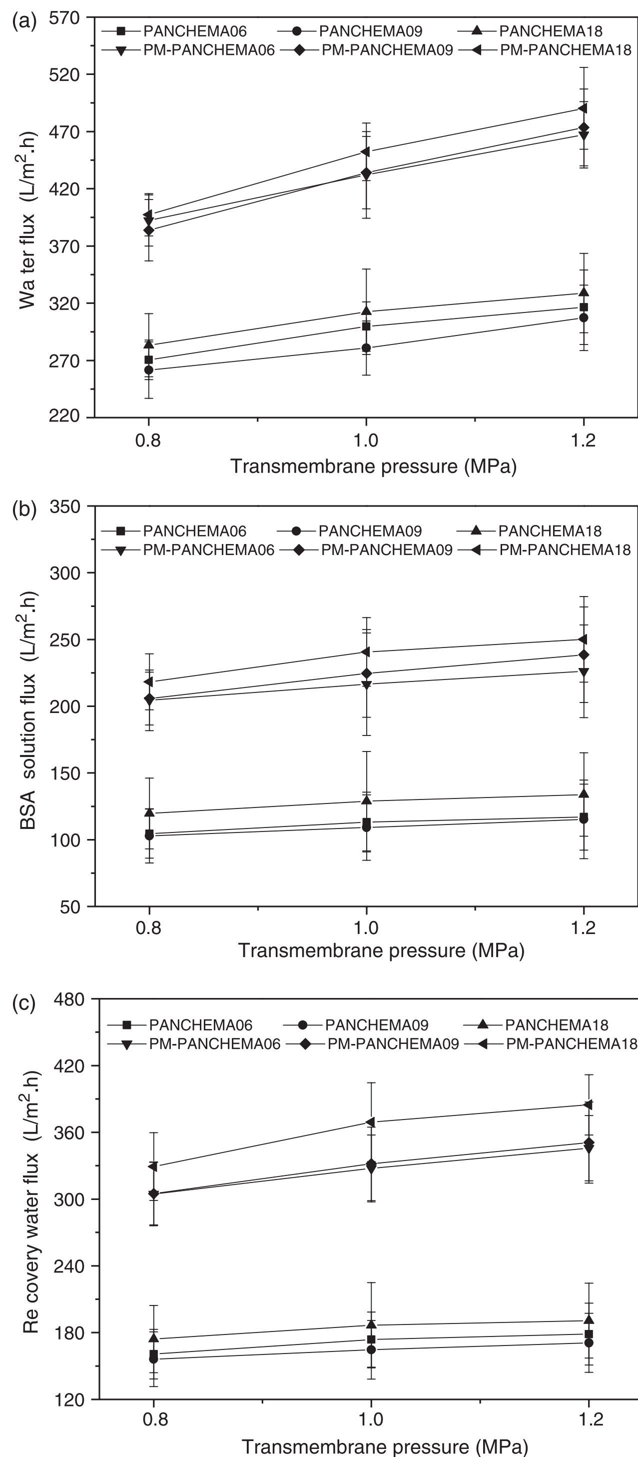

Fig. 9. Permeation fluxes of pure water (a), BSA solution (b), and water after chemical cleaning (c) through PANCHEMA and PM-PANCHEMA membranes under different transmembrane pressure.

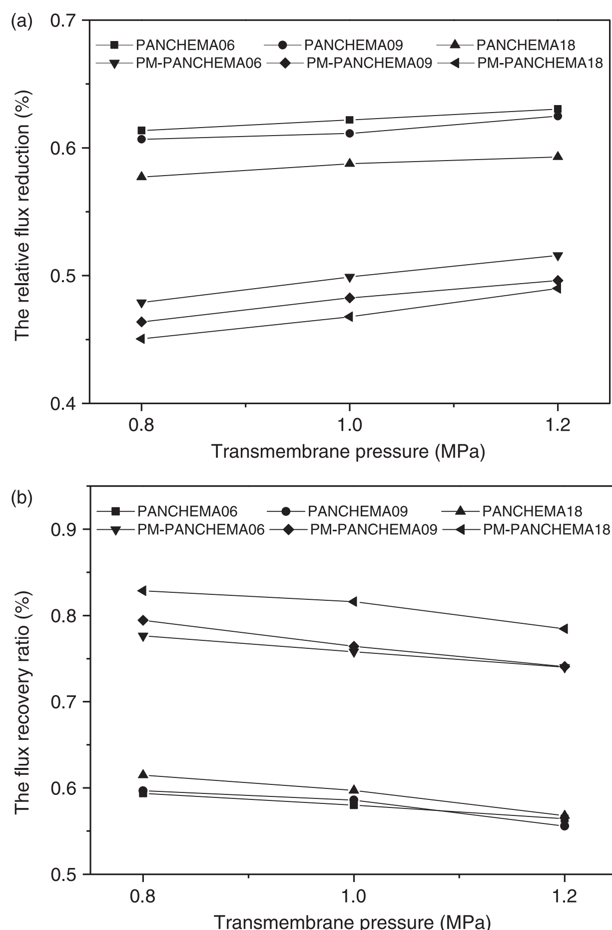

Fig. 10. Flux changes of the PANCHEMA and PM-PANCHEMA membranes during filtration and after chemical cleaning: the relative flux reduction (a) and the flux recovery ratio (b).

when they are adsorbed on the membrane surface or contact with the membrane surface. These results prove that the biocompatibility of the PAN-based membranes could be improved efficiently by anchoring phospholipid moieties on the membrane surface.

3.3. Permeation and antifouling properties

To investigate the filtration performance of the membranes, water and BSA solution filtration experiments were carried out. Typical results for permeation fluxes through the PANCHEMA and PM-PANCHEMA membranes are depicted in Figs. 8 and 9. It was found that there is no obvious change on the BSA rejection before and after the conducted modification. However, the fluxes of water (J_w) and BSA solution (J_p) for the PM-PANCHEMA membranes are obviously higher than that for the PANCHEMA under different flux rate (Fig. 9(a) and (b)). It can be revealed that the PM-PANCHEMA membrane surface become more hydrophilic by the introduction of phospholipid moieties. And when the membrane surface contacted with protein solution, the phospholipid moieties can be hydrated, these hydrated moieties on the surface have exerted hydrodynamics and steric hindrance effects to the approaching of protein. The effect of chemical cleaning on the membrane filtration performance is shown in Fig. 9(c). In this figure, the water permeation flux after cleaning (J_R) is presented. It was found that the similar result can be obtained, and J_R is slightly increased with the increase of phospholipid moieties on the membrane surface under different flux rate, which agrees with the results based on water contact angle measurement. This is reasonable because of the protein on the hydrophilized PM-PANCHEMA membrane surface can be removed more easily by chemical cleaning.

Fig. 10 shows the percent of relative flux reduction (RFR) by protein fouling and flux recovery ratio (FRR) by chemical cleaning. It can be seen that the relative flux reduction (RFR) increases with the increase of transmembrane pressure. This result implies that membrane fouling is depended on the flow rate, which is mainly attributed to the concentration polarization and unavoidable. While both of RFR and FRR for the PM-PANCHEMA membranes are obviously higher than that for PANCHEMA membranes. Furthermore, a relatively high flux recovery ratio (FRR > 75%) has been achieved on the PM-PANCHEMA membranes. All these results indicate that the antifouling properties of the PANCHEMA membrane can be improved efficiently by the introduction of phospholipid moieties onto the membrane surface.

4. Conclusion

Phospholipid moieties could be directly anchored on the PAN-based membrane surface with the described process. The chemical and morphological changes of the modified membranes surfaces have been confirmed by FT-IR/ATR, XPS and SEM. The decrease of the water contact angles and the increase of the water flux for the PM-PANCHEMA membranes indicate the improvement of the surface hydrophilicity by the introduction of phospholipid moieties. Results in BSA solution permeation and cell adhesion experiments imply strongly that a considerable enhancement of biocompatibility can be achieved.

Acknowledgements

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